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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,796	07/23/2001	Catherine Taylor	10799/13	2704

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	10

DATE MAILED: 11/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/909,796	Taylor et al.
Examiner	**Art Unit**
Mary Schmidt	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Aug 16, 2002* .

2a) [ ] This action is **FINAL**. 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *1-6, 10, 11, 19-23, 31-33, 37, 38, and 46-50* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *1-6, 10, 11, 19-23, 31-33, 37, 38, and 46-50* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [X] The drawing(s) filed on _____ is/are a) [X] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____ .
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [X] Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9 & 11
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other: #9 dated 9/24; #11 dated 9/25

DETAILED ACTION

1. Applicant's election without traverse of Group I, drawn to methods of modulating apoptosis with an agent, wherein the agent is a chemical drug (non-nucleic acid), with the species election of 1,4-Diaminobutane (putrescine) as the non-nucleic acid drug, in Paper No. 8B, filed August 16, 2002, is acknowledged. The elected claims are examined on the merits below for the methods comprising administration of the elected drug species, 1,4-Diaminobutane (putrescine).

Drawings

2. The drawings, figures 1-21, in the specification as filed have been reviewed by an official draftsman and found acceptable.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3-6, 10, 11, 19, 21-23, 30-33, 37, 38, and 46-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for modulating apoptosis *in vitro* (both cells in cell culture and cell free assays) comprising the step of administering *in vitro* the agent putrescine, does not reasonably provide enablement for methods for modulating apoptosis in a cell in a mammal comprising the step of administering to the

mammal the agent putrescine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 3-6, 10, 11, 19, 21-23, 30-33, 37, 38, and 46-50 are rejected for the scope of the claims drawn to methods for modulating apoptosis in a cell or in a mammal comprising the step of administering to said cell an agent that inhibits apoptosis-induced eIF-5A or DHS function when the cell is a cell in a mammal and not in cell culture. Claim 46 specifies that the mammal is human. Claim 47 specifies that the administration is by intraperitoneal injection.

MPEP 2164.01(a) lists the factors for determining "whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) the amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)"

In the instant case, the role of putrescine (a well-known polyamine) in modulating apoptosis in cells is described in the scientific literature as highly complex and ambiguous. Schipper et al. (Cancer Biology, Vol. 0, 2000; pp. 55-68) is a review entitled "Involvement of polyamines in apoptosis. Facts and controversies: effectors or protectors?" In fact, the instant

specification on pages 7 and 9 teaches this ambiguity, where in some instances polyamines have been show to protect cells from the induction of apoptosis (page 7, lines 7-23), while in other instances, the induction of apoptosis has been observed in response to exogenous polyamines (page 8, lines 3-8). Table 1 (page 58) of Schipper et al. further compares results in the prior art for a correlation between induction of apoptosis and putrescine levels.

The instant claims are drawn to modulating apoptosis by administration of putrescine. Modulating indicates either an increase or a decrease in apoptosis. In the instant case the prior art indicates that putrescine may be involved in either direction depending on the complex environmental circumstances and the complex interactions underlying regulation of cell growth, cell arrest or cell death. One of skill in the art would have recognized that the complex mechanisms of cell regulation had not been elucidated at the time of filing of the instant specification, and that further understanding of the basic research surrounding the involvement of putrescine in apoptosis hinged on unraveling the complex molecular pathways involving cell regulation. The following references are cited to provide a background understanding of the observations made in the literature regarding the role of putrescine in apoptosis: (1) Monti et al. (Life sciences, Vol. 62, No. 9, pp. 799-806, 1998) taught that "In contrast to previous studies, exogenous polyamines failed to protect HL-60 cells against apoptosis caused by dRib.... depletion of intracellular levels of putrescine and spermidine by ... (DMFO) delayed the onset of apoptosis by at least a day or so. Exogenous polyamines reversed the beneficial effect of DMFO and restored the apoptotic levels observed in dRib-treated cells. We suggested that polyamines,

especially putrescine and spermidine, act as facilitating factors in the induction of apoptosis triggered by dRib in HL-60 cells." (Abstract); (2) similarly, Monti et al. (Biochem. Biophys. Res. Commun. 257, 460-465, 1999) further taught that "The presence of polyamines is required for the apoptotic program triggered by 2-deoxy-D-ribose (dRib) in HL-60 cells.... The present study points to a relationship between spermidine-induced G1 to S phase transition and the onset of dRib-induced apoptosis. Conversely, the G1 block induced by ... (DMFO) is associated with a protective effect against dRib-induced cell suicide. Replenishment of the intracellular spermidine pool by exogenous putrescine and spermidine induces cell cycle progression and restores apoptotic levels." (Abstract); (3) Lopez et al. (Biocell, 1999, 23 (3), 223-228) and Sakagami et al. (Anticancer Research 20, 265-270, 2000) both follow the concentration level changes in polyamines in CHO and HL-60 cells respectively during apoptosis. Lopez et al. teaches on page 223 that "Polyamines, naturally occurring polycations in cells, are required for many growth-related processes, including normal cell cycle progression, cell proliferation and differentiation.... While these molecules are critical for optimal cell growth, excessive concentrations of highly charged polyamines may interfere directly with normal cell function.... In this sense, toxicity of these amines has been demonstrated in a number of mammalian cells.... They have been recently implicated in apoptosis...." Sakagami et al. further teaches in the abstract that "The present study demonstrates that the putrescine level is the most sensitive to the proliferation capability of the cells, among [the] three polyamines, and provides an early marker for apoptosis and proliferation."; (4) Ha et al. (Biochem. Biophys. Res. Commun. 244, 298-303,

1998) further state the ubiquitous nature of polyamines: "The naturally occurring polycationic polyamines spermine, spermidine, and their diamine precursor putrescine are found in all eukaryotic cells. Intracellular polyamines are essential for cell proliferation and differentiation, and the intracellular concentration of these ubiquitous molecules is highly regulated by their metabolic pathway.... Some of the roles ascribed to polyamines include preventing endonuclease-mediated DNA fragmentation... and inhibiting damage caused by alkylating agents..., singlet oxygen... and radiation.... Depletion of intracellular polyamines by inhibiting polyamine biosynthesis with 2-difluoromethylornithine or by inducing polyamine catabolism with polyamine analogues results in alteration of chromatin and DNA structure and may in some cases result in programmed cell death...." (Page 298); (5) Ratasirayakorn et al. (J. Of Periodontology, Feb. 1999, 70 (2), p179-84) taught that administration of 1mM putrescine for 1 hour to polymorphonuclear leukocytes in culture protected the cells from apoptosis (see abstract).

The instant specification as filed does not teach by way of example administration of putrescine to cells in cell culture or in cells in a whole organism. The specification as filed teaches by way of example screening for and isolation of a novel rat gene (Examples 1-4). The specification further teaches in Examples 5 and 6 administration of spermidine to rats, and determination of apoptosis levels, but does not teach any administration of putrescine by for methods of modulating apoptosis as claimed.

The prior art further taught that while putrescine is common in many foods, when systemically administered putrescine can be toxic. U.S. Patent 6,258,845, teaches in col. 8, lines

21-27, that "putrescine is present in many common foods, such as orange juice, which contains approximately 400 ppm putrescine." Camon et al. (NeuroToxicology 15 (3), 759-764, 1994) taught that "After ip injection of PUT to the rat, only minor behavioral effects have been described (Genedani et al., 1984, 1987; Ferchmin and Eterovic, 1990). In these studies no overt signs of toxicity were observed in a dose range of 100-400 mg/kg. However, in a previous work (de Vera et al., 1992) we reported toxic response which includes, besides shaking behavior, severe atony and death of some animals. Nevertheless, the observed effects had a great interindividual variability." (Page 759) In the 1994 NeuroTox. reference, on page 761, they taught that "A non-lethal dose of 150mg/kg PUT... was used.... Thirty three percent of the animals showed behavioral signs of toxicity...." They further taught on page 762 that "In our conditions, the motor disorders increased in a dose dependent-manner and, at 200 mg/kg, were so severe that some animals died, probably due to respiratory arrest.... Some signs described in this study (hyperexcitability and WDS) are related to CNS actions of PUT..., while the motor disturbances could also [be] due to some peripheral actions of this polyamine. Relaxing effects of polyamines on skeletal muscle and blockade of neuromuscular junction have been reported (Seiler, 1991). However, the severity of the motor perivascular and cellular edema has been described after PUT in different brain regions.... The relationship between brain PUT concentrations and clinical status suggests that the differences observed in the response to PUT could be due to kinetic factors, among which the capacity to cross the blood-brain barrier may be

crucial. Koenig et al. (1989) have reported that PUT synthesis is involved in the opening of the blood-brain barrier."

MPEP 2164.01 c. teaches that "it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation.... A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved....Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art." MPEP 2164.03 states that "The scope of the required enablement varies inversely with the degree of predictability involved.... In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required." MPEP 2164.04 further states that "The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled int eh art is not commensurate with the scope of protection sought by the claims."

The instant specification as filed has not provided any direction for how to use the claimed invention in cells in a mammal. Specifically the factors such as how to administer the putrescine to a mammal for the functions claimed, including factors such as concentration, route of administration, and the types of target cells to be regulated by such administration have not been shown so that the desired modulation of apoptosis, and the specific regulation of eif-5a or

DHS as claimed is achieved by administration of the putrescine. The prior art suggests that low levels of putrescine in common foods are acceptable, although these amounts do not clearly effect the claimed functions of modulating apoptosis. The teachings of Camon et al. strongly correlate higher levels of putrescine directly administered to undesired toxic effects on the nervous system. Absent further guidance, one skilled in the art would not accept the ability to selectively increase or decrease apoptosis in a mammal in a desired manner due to the extreme sensitivity and complexity of the cell-regulatory mechanisms, the ubiquitous nature of putrescine in every cell in the mammal, and the complex role it has in the balance of cell growth or death. One of skill in the art would recognize that the state of the art at the time the specification was filed recognized the role of putrescine in apoptosis, but did not teach the underlying mechanism, nor the ability to modulate its effects on apoptosis *in vivo*, nor provide therapeutic effects for the diseases listed on page 10 of the specification, lines 7-17 (an asserted utility of the instant methods). The use of cells in cell culture conditions where endogenous putrescine is administered, does not provide a clear teaching of a nexus to the results expected upon administration of putrescine to cells in a mammal. It would require "trial and error" experimentation for one skilled in the art to further elucidate the effects of putrescine administration to different mammals, including human, for modulating apoptosis. For instance, if apoptosis is desired in cancer cells, what type of cancer in a mammal would putrescine administration effect? Since putrescine is ubiquitously expressed, would amounts sufficient to induce apoptosis in the cancer cells cause toxicity and apoptosis in the non-cancer cells? Since

only a general teaching of the nexus of apoptosis and putrescine regulation is taught in the prior art, and since the examples in specification as filed are not predictive of administration of putrescine to cells in a mammal for the claimed functions (including the asserted therapeutic functions listed on page 10 of the specification), one of skill in the art would necessarily practice undue experimentation to make and use the claimed methods in a mammal.

5. Claims 4, 10, 11, 22, 23 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 4, 10, 11, 22, 23 and 31 are not considered enabled for their methods of specifically inhibiting the transcription of eIF-5A via administration of putrescine or inhibiting DHS transcription or translation via administration of putrescine.

Claim 4 specifies the method of claim 1, wherein said agent inhibits transcription of an apoptosis-induced eIF-5A gene. Claim 10 specifies the method of claim 4, wherein said agent comprises a chemical or drug capable of inhibiting activation of an apoptosis-induced eIF-5A protein by apoptosis-induced DHS. Claim 11 specifies the method of claim 10, wherein said chemical or drug comprises 1,4-diamino-butane (putrescine). Claim 22 specifies the method of claim 19, wherein said agent inhibits transcription of an apoptosis-induced DHS gene. Claim 23 specifies the method of claim 19, wherein said agent inhibits translation of an apoptosis-induced

DHS gene transcript. Note that DHS is described on page 2 of the specification as deoxyhypusine synthase. Claim 31 is drawn to the method of claim 30 wherein said agent inhibits transcription of an apoptosis-induced eIF-5A gene in said target cells of said mammal.

Tome et al. (Biochem. J. 1997, 328, 847-854) and (Biol. Signals, 1997, 6, 150-156) performed experiments which taught that putrescine inhibition of eIF-5A was not at the level of transcription. In Biochem. J., page 851, col. 2, lines 19-25 (last para.), it was taught that elevated putrescine levels did not affect the eIF-5A mRNA content and "no suppression or elevation of eIF-5A mRNA levels occurs in correlation with the increased endogenous putrescine." In Biol. Signals, pages 153, col. 2, lines 39-41, and page 154, col. 1, lines 1-6, they taught that "The effects of putrescine on the formation of modified eIF-5A appear to be postranscriptional because excess putrescine does not suppress cellular eIF-5A mRNA. Excess putrescine may inhibit eIF-5A mRNA translation or may stimulate the degradation of modified or unmodified eIF-5A (or both)." Although Tome et al. taught that "both diaminoheptane and excess putrescine accumulation appear to induce apoptosis by suppressing the formation of hypusine-containing eIF-5A...." on page 153, col. 2, lines 22-25, and on page 152, col. 1, lines 28-39, the nexus between polyamines and hypusine synthesis, they did not teach that putrescine acts to inhibit deoxyhypusine synthase (DHS) gene transcription or translation (instant claims 22 and 23).

Neither the specification nor the prior art taught an expectation of success for administration of putrescine to cells or mammals for methods of specifically inhibiting the gene transcription of eIF-5A or inhibiting DHS gene transcription or translation. Tome et al. taught

away from the mechanism of putrescine acting on eIF-5A at the level of transcription. One of skill in the art would necessarily practice basic research to further elucidate the mechanism of action of putrescine on DHS transcription and translation, since this information is missing from the specification and the prior art. It would require *de novo* experimentation to practice the claimed methods having these claimed steps since one of skill in the art would recognize from the relevant literature, that putrescine was not known at the time of filing to function via inhibition of eIF-5A gene transcription nor inhibition of DHS gene transcription or translation. One of skill in the art at the time the invention was made would necessarily have to practice undue experimentation to use putrescine for these specific functions in the absence of further guidance or teaching showing, for instance, that the teachings of Tome et al. are not uniform in other cell types, or cell environments.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 2, 3, 6, 19, 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Tome et al. (Biochem. J. 1997, 328, 847-854).

Claim 1 is drawn to a method for modulating apoptosis in a cell comprising the step of administering to said cell an agent that inhibits apoptosis-induced function in said cell. Claim 2 specifies the method of claim 1, wherein said administering is performed *in vitro*. Claim 3 specifies the method of claim 1, wherein said administering is performed *in vivo*. Claim 6 specifies the method of claim 1, wherein said agent inhibits activation of an apoptosis-induced eIF-5A protein. Claim 19 is drawn to a method for modulating apoptosis in a cell comprising the step of administering to said cell an agent that inhibits apoptosis-induced DHS function in said cell. Claim 20 specifies the method of claim 19, wherein said administering is performed *in vitro*. Claim 21 specifies the method of claim 19, wherein said administering is performed *in vivo*. Note that DHS is described on page 2 of the specification as deoxyhypusine synthase.

Tome et al. taught administration of exogenous putrescine to DH23A cells in cell culture for results "suggesting that putrescine is a causative agent or trigger of apoptosis." (Abstract) They called this administration to cells in cell culture, "in vivo" (instant claims 3 and 21), to distinguish this administration from the experiments performed in the cell-free environments which they term "in vitro" (see page 851, col. 1, lines 15-18 for instance). They teach the direct nexus between putrescine and eIF-5A and the formation of hypusine: "Accumulation of excess intracellular putrescine inhibits the formation of hypusine *in vivo* (in cells in cell culture), a reaction that proceeds by the transfer of the butylamine moiety of spermidine to a lysine residue in eukaryotic initiation factor 5A (eIF-5A)." (Abstract) They taught on page 848, col. 2, last para., that "Cells treated with exogenous putrescine accumulate putrescine and enter cytostasis

more quickly than those in cultures where putrescine accumulates through endogenous production." They taught on page 849, col. 2, that "The addition of exogenous putrescine mimics the effect of endogenous putrescine production on cell growth kinetics, endogenous putrescine and apoptosis...." They taught on page 851, col. 1, lines 11-39, that "putrescine addition inhibits the formation of modified eIF-5A...." They further taught on page 851, col. 2, lines 19-25 (last para.) that elevated putrescine levels did not affect the eIF-5A mRNA content and "no suppression or elevation of eIF-5A mRNA levels occurs in correlation with the increased endogenous putrescine." They taught that the eIF-5A was not activated because it remained unmodified. Therefore, such findings rule out that the putrescine functions via inhibition of transcription or translation of eIF-5A or DHS (instant claims 4, 5, 10, 11, 22 and 23). Tome et al. thus teach the claimed invention of modulating apoptosis, specifically showing a correlation between addition of putrescine to cells in cell culture, decrease in eIF-5A modified form, and an induction of apoptosis.

Claims 19-21 are included in the instant rejection because the functional language "inhibits apoptosis-induced DHS function" does not breath further like and meaning into the claimed methods of administration of putrescine to cells. MPEP 2112.01 states that "[p]roducts of identical chemical composition can not have mutually exclusive properties." Since Tome et al. taught the effect of putrescine on eIF-5A was to "inhibit the formation of hypusine..., a reaction that proceeds by the transfer of the butylamine moiety of spermidine to a lysine residue in... eIF-5A", they taught that it was a property of putrescine to inhibit the normal function of

deoxyhypusine synthase (DHS) either directly or indirectly. Therefore, Tome et al. also taught that putrescine administration was capable of inhibiting "apoptosis-induced DHS" in the treated cells.

8. Claims 1, 2, 5, 6, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Tome et al. (Biol. Signals, 1997, 6, 150-156).

Claim 1 is drawn to a method for modulating apoptosis in a cell comprising the step of administering to said cell an agent that inhibits apoptosis-induced function in said cell. Claim 2 specifies the method of claim 1, wherein said administering is performed *in vitro*. Claim 5 specifies wherein said agent inhibits translation of an apoptosis-induced eIF-5A gene transcript. Claim 6 specifies the method of claim 1, wherein said agent inhibits activation of an apoptosis-induced eIF-5A protein. Claim 19 is drawn to a method for modulating apoptosis in a cell comprising the step of administering to said cell an agent that inhibits apoptosis-induced DHS function in said cell. Claim 20 specifies the method of claim 19, wherein said administering is performed *in vitro*. Note that DHS is described on page 2 of the specification as deoxyhypusine synthase.

Tome et al. taught administration of exogenous putrescine to DH23A/b cells in cell culture. (Abstract) In this reference they refer to the cells in cell culture, as "in vitro" (page 153, col. 1, line 4. They taught on page 152, col. 2, lines 34-40, that "recent data suggest that inhibition of the formation of modified eIF-5A may also play a role in putrescine-induced

apoptosis." They taught on page 153, col. 2, lines 5-10, that "[t]he mechanism by which putrescine over-accumulation induces apoptosis in DH23A/b cells appears to involve the suppression of hypusine formation in eIF-5A. On pages 153, col. 2, lines 39-41, and page 154, col. 1, lines 1-6, they state that "The effects of putrescine on the formation of modified eIF-5A appear to be postranscriptional because excess putrescine does not suppress cellular eIF-5A mRNA. Excess putrescine may inhibit eIF-5A mRNA translation or may stimulate the degradation of modified or unmodified eIF-5A (or both)." Claims 19-21 are included in the instant rejection because the functional language "inhibits apoptosis-induced DHS function" does not breath further like and meaning into the claimed methods of administration of putrescine to cells. MPEP 2112.01 states that "[p]roducts of identical chemical composition can not have mutually exclusive properties." Since Tome et al. taught that "both diaminoheptane and excess putrescine accumulation appear to induce apoptosis by suppressing the formation of hypusine-containing eIF-5A...." on page 153, col. 2, lines 22-25, and on page 152, col. 1, lines 28-39, the nexus between polyamines and hypusine synthesis, they taught that it was a property of putrescine to inhibit the normal role either directly or indirectly of deoxyhypusine synthase (DHS). Therefore, Tome et al. also taught that putrescine administration was capable of inhibiting "apoptosis-induced DHS" in the treated cells.

9. Claims 30-33, 37, 38, and 46-50 are free of the prior art because the prior art did not teach nor fairly suggest administration of putrescine to whole organism mammals for the claimed

methods of modulating apoptosis. Claims 4, 10 and 11 are considered free of the closest prior art (both Tome et al. references cited above under 35 U.S.C. 102(b)) since Tome et al. specifically taught away from putrescine inhibition of transcription of eIF-5A. Furthermore, claims 22 and 23 are free of the prior art since the prior art did not teach nor fairly suggest inhibition of the DHS gene transcript as a result of putrescine administration to cells for modulation of apoptosis.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

M. M. Schmidt
November 4, 2002